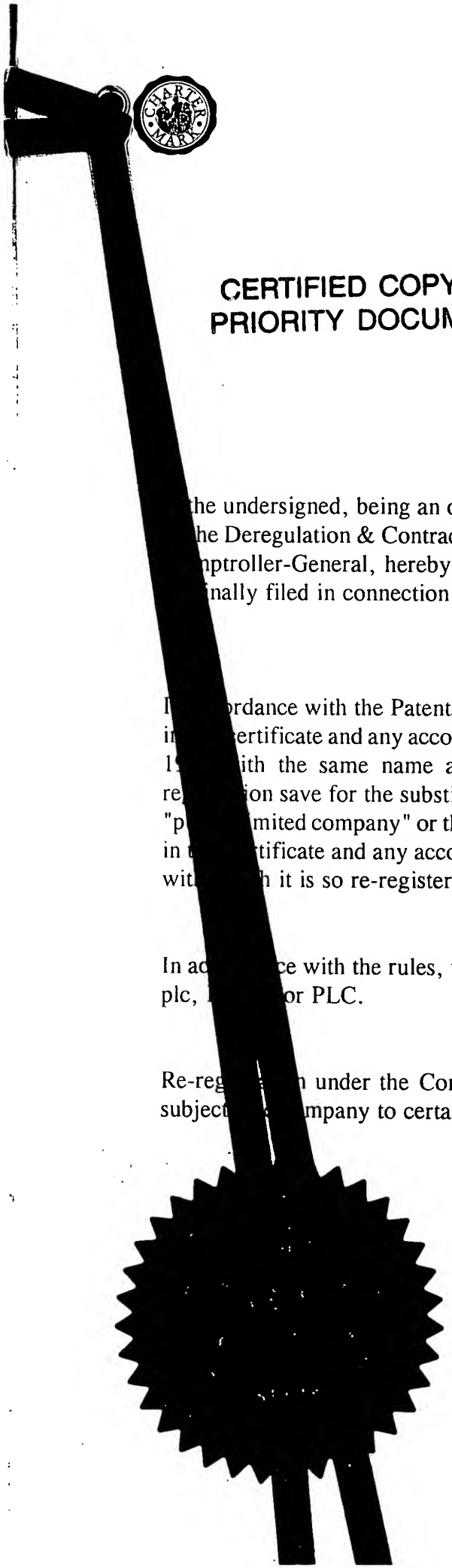

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Signed Andrew Cregg

Dated 29 January 2001

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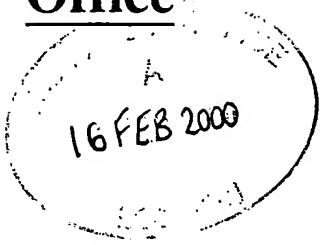

1/77

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P01/7700 0.00-0003636.8

Request for grant of a patent

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1. Your reference — ACC/JR/P32510

2. Patent application number
(The Patent Office will fill in his part)
16 FEB 2000
0003636.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

SmithKline Beecham plc
New Horizons Court, Brentford, Middx TW8 9EP,
Great Britain

7605058001

United Kingdom

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Patents ADP number *(if you know it)*

CORPORATE INTELLECTUAL PROPERTY

SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

8800974004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

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Continuation sheets of this form	
Description	31
Claim(s)	4
Abstract	
Drawings	

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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 1/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature A C Connell Date 14-Feb-00

A C Connell

12. Name and daytime telephone number of person to contact in the United Kingdom: A C Connell 01279 644395

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Novel Compounds

The present invention relates to certain novel pyrimidinone compounds, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them and their use in therapy, in particular in the treatment of atherosclerosis.

WO 95/00649 (SmithKline Beecham plc) describe the phospholipase A2 enzyme Lipoprotein Associated Phospholipase A_2 (Lp-PLA_2), the sequence, isolation and purification thereof, isolated nucleic acids encoding the enzyme, and recombinant host cells transformed with DNA encoding the enzyme. Suggested therapeutic uses for inhibitors of the enzyme included atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. A subsequent publication from the same group further describes this enzyme (Tew D *et al*, Arterioscler Thromb Vas Biol 1996:16;591-9) wherein it is referred to as LDL-PLA_2. A later patent application (WO 95/09921, Icos Corporation) and a related publication in Nature (Tjoelker *et al*, vol 374, 6 April 1995, 549) describe the enzyme PAF-AH which has essentially the same sequence as Lp-PLA_2 and suggest that it may have potential as a therapeutic protein for regulating pathological inflammatory events.

It has been shown that Lp-PLA_2 is responsible for the conversion of phosphatidylcholine to lysophosphatidylcholine, during the conversion of low density lipoprotein (LDL) to its oxidised form. The enzyme is known to hydrolyse the sn-2 ester of the oxidised phosphatidylcholine to give lysophosphatidylcholine and an oxidatively modified fatty acid. Both products of Lp-PLA_2 action are biologically active with lysophosphatidylcholine, a component of oxidised LDL, known to be a potent chemoattractant for circulating monocytes. As such, lysophosphatidylcholine is thought play a significant role in atherosclerosis by being responsible for the accumulation of cells loaded with cholesterol ester in the arteries. Inhibition of the Lp-PLA_2 enzyme would therefore be expected to stop the build up of these macrophage enriched lesions (by inhibition of the formation of lysophosphatidylcholine and oxidised free fatty acids) and so be useful in the treatment of atherosclerosis.

The increased lysophosphatidylcholine content of oxidatively modified LDL is also thought to be responsible for the endothelial dysfunction observed in patients with atherosclerosis. Inhibitors of Lp-PLA_2 could therefore prove beneficial in the treatment of this phenomenon. An Lp-PLA_2 inhibitor could also find utility in other disease states that exhibit endothelial dysfunction including diabetes, hypertension, angina pectoris and after ischaemia and reperfusion.

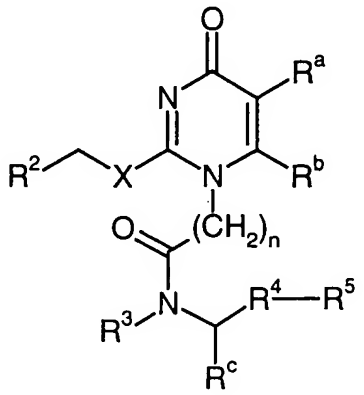
In addition, Lp-PLA_2 inhibitors may also have a general application in any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA_2. Examples of such disorders include psoriasis.

Furthermore, Lp-PLA_2 inhibitors may also have a general application in any disorder that involves lipid oxidation in conjunction with Lp-PLA_2 activity to produce the two injurious products, lysophosphatidylcholine and oxidatively modified fatty acids. Such conditions include the aforementioned conditions atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia (see Psychopharmacology Bulletin, 31, 159-165, 1995).

Patent applications WO 96/12963, WO 96/13484, WO96/19451, WO 97/02242, WO97/217675, WO97/217676, WO 96/41098, and WO97/41099 (SmithKline Beecham plc) disclose *inter alia* various series of 4-thionyl/sulfinyl/sulfonyl azetidinone compounds which are inhibitors of the enzyme Lp-PLA_2. These are irreversible, acylating inhibitors (Tew *et al*, Biochemistry, **37**, 10087, 1998).

A new class of compounds has now been identified which are inhibitors of the enzyme Lp-PLA_2.

Accordingly, the present invention provides a compound of formula (I):



(I)

in which:

R^a is hydrogen, halogen, $C_{(1-3)}$alkyl, $C_{(1-3)}$alkoxy, hydroxy$C_{(1-3)}$alkyl, $C_{(1-3)}$alkylthio, $C_{(1-3)}$alkylsulphinyl, amino$C_{(1-3)}$alkyl, mono- or di-$C_{(1-3)}$alkylamino$C_{(1-3)}$alkyl, $C_{(1-3)}$alkylcarbonylamino$C_{(1-3)}$alkyl, $C_{(1-3)}$alkoxy$C_{(1-3)}$alkylcarbonylamino$C_{(1-3)}$alkyl, $C_{(1-3)}$alkylsulphonylamino$C_{(1-3)}$alkyl, $C_{(1-3)}$alkylcarboxy, or $C_{(1-3)}$alkylcarboxy$C_{(1-3)}$alkyl;

R^b is hydrogen, halogen, $C_{(1-3)}$alkyl, or hydroxy$C_{(1-3)}$alkyl, with the proviso that R^a and R^b are not simultaneously each hydrogen; or

R^a and R^b together are $(CH_2)_n$ where n is 3 or 4, to form, with the pyrimidine ring carbon atoms to which they are attached a fused 5-or 6-membered carbocyclic ring;

R^c is hydrogen or $C_{(1-3)}$alkyl;

R^2 is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$alkyl, $C_{(1-18)}$alkoxy, $C_{(1-18)}$alkylthio, aryl$C_{(1-18)}$alkoxy, hydroxy, halogen, CN, COR^6, carboxy, $COOR^6$, NR^6COR^7, $CONR^8R^9$, $SO_2NR^8R^9$, $NR^6SO_2R^7$, NR^8R^9, mono to perfluoro-$C_{(1-4)}$alkyl, mono to perfluoro-$C_{(1-4)}$alkoxyaryl, and aryl$C_{(1-4)}$alkyl;

R^3 is hydrogen or $C_{(1-4)}$alkyl which may be unsubstituted or substituted by hydroxy, OR^6, COR^6, carboxy, $COOR^6$, $CONR^8R^9$, NR^8R^9, mono- or di-(hydroxy$C_{(1-6)}$alkyl)amino or N-hydroxy$C_{(1-6)}$alkyl-N-$C_{(1-6)}$alkyl amino;

R^4 is an aryl or a heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$alkyl, $C_{(1-18)}$alkoxy, $C_{(1-18)}$alkylthio, aryl$C_{(1-18)}$alkoxy, hydroxy, halogen, CN, COR^6, carboxy, $COOR^6$, NR^6COR^7, $CONR^8R^9$, $SO_2NR^8R^9$, $NR^6SO_2R^7$, NR^8R^9, mono to perfluoro-$C_{(1-4)}$alkyl and mono to perfluoro-$C_{(1-4)}$alkoxy;

R^5 is an aryl ring which is further optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$alkyl, $C_{(1-18)}$alkoxy, $C_{(1-18)}$alkylthio, aryl$C_{(1-18)}$alkoxy, hydroxy, halogen, CN, COR^6, carboxy, $COOR^6$, $CONR^8R^9$, NR^6COR^7, $SO_2NR^8R^9$, $NR^6SO_2R^7$, NR^8R^9, mono to perfluoro-$C_{(1-4)}$alkyl and mono to perfluoro-$C_{(1-4)}$alkoxy;

R^6 and R^7 are independently hydrogen or $C_{(1-20)}$alkyl, for instance $C_{(1-4)}$alkyl (e.g. methyl or ethyl);

R^8 and R^9 which may be the same or different is each selected from hydrogen, $C_{(1-12)}$alkyl, CH_2R^{10}, $CHR^{11}CO_2H$ or a salt thereof, or R^8 and R^9 together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing one or more further heteroatoms selected from oxygen, nitrogen and sulphur, and optionally substituted by one or two substituents selected from hydroxy, oxo, $C_{(1-4)}$alkyl, $C_{(1-4)}$alkylCO, aryl, e.g. phenyl, or aralkyl, e.g benzyl, for instance morpholine or piperazine;

R^{10} is COOH or a salt thereof, $COOR^{12}$, $CONR^6R^7$, CN, CH_2OH or CH_2OR^6;

R^{11} is an amino acid side chain such as CH_2OH from serine;

R^{12} is $C_{(1-4)}$alkyl or a pharmaceutically acceptable *in vivo* hydrolysable ester group;

n is an integer from 1 to 4, preferably 1 or 3;

X is O or S.

Representative examples of R^a include chloro, bromo, methyl, ethyl, n-propyl, methoxy, hydroxymethyl, hydroxyethyl, methylthio, methylsulphinyl, aminoethyl, dimethylaminomethyl, acetylaminoethyl, 2-(methoxyacetamido)ethyl, mesylaminoethyl, ethylcarboxy, and iso-propylcarboxymethyl.

Representative examples of R^b include hydrogen, and methyl.

Preferably R^a is methyl or ethyl and R^b is hydrogen or methyl, or R^a and R^b together with the pyrimidine ring carbon atoms to which they are attached form a fused 5-or 6-membered carbocyclic ring.

Representative examples of R^c include hydrogen and methyl.

Preferably X is S.

Representative examples of R^2 when an aryl group include phenyl and naphthyl. Representative examples of R^2 when a heteroaryl group include pyridyl, pyrimidinyl, pyrazolyl, furanyl, thienyl, thiazolyl, quinolyl, benzothiazolyl, pyridazolyl and pyrazinyl. Preferably, R^2 is phenyl optionally substituted by halogen.

Representative examples of R^2CH_2X include 4-fluorobenzylthio.

Representative examples of R^3 include hydrogen, methyl, 2-(diethylamino)ethyl and piperidinoethyl.

Representative examples of R^4 include phenyl, pyridine and pyrimidine.

Representative examples of R^5 include phenyl optionally substituted by halogen, or trifluoromethyl, preferably at the 4-position.

Preferably, R^4 and R^5 together form a 4-(phenyl)phenyl or a 2-(phenyl)pyridinyl substituent in which the remote phenyl ring may be optionally substituted by halogen or trifluoromethyl, preferably at the 4-position.

Pharmaceutically acceptable *in vivo* hydrolysable ester groups for R^{12} include those which break down readily in the human body to leave the parent acid or its salt.

Representative examples of values of pharmaceutically acceptable *in vivo* hydrolysable ester groups for R^{12} include:

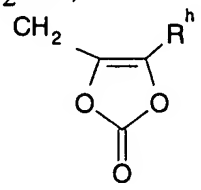
$-CH(R^{aa})O.CO.R^{bb}$;

$-CH(R^{aa})O.CO.OR^{cc}$;

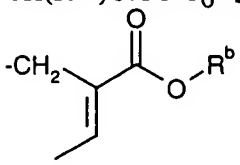
$-CH(R^{aa})CO.NR^eR^f$

$-R^dNR^eR^f$;

$-CH_2OR^g$;



$CH(R^{aa})O.CO.C_6H_4Y^1COCH(R^i)NH_2$; and



in which:

R^{aa} is hydrogen, $(C_1\text{-}6)$alkyl, in particular methyl, $(C_3\text{-}7)$cycloalkyl, or phenyl, each of which may be optionally substituted;

R^{bb} is $(C_1\text{-}6)$alkyl, $(C_1\text{-}6)$alkoxy$(C_1\text{-}6)$alkyl, phenyl, benzyl, $(C_3\text{-}7)$cycloalkyl, $(C_1\text{-}6)$alkyl$(C_3\text{-}7)$cycloalkyl, 1-amino$(C_1\text{-}6)$alkyl, or 1-$(C_1\text{-}6$alkyl)amino$(C_1\text{-}6)$alkyl, each of which may be optionally substituted; or

R^{aa} and R^{bb} together form a 1,2-phenylene group optionally substituted by one or two methoxy groups;

R^{cc} is $(C_1\text{-}6)$alkyl, $(C_3\text{-}7)$cycloalkyl, $(C_1\text{-}6)$alkyl$(C_3\text{-}7)$cycloalkyl;

R^d is $(C_1\text{-}6)$alkylene optionally substituted with a methyl or ethyl group;

R^e and R^f which may be the same or different is each $(C_1\text{-}6)$alkyl; or aryl$(C_1\text{-}4)$ alkyl, optionally substituted with e.g. hydroxy;

R^g is $(C_1\text{-}6)$alkyl;

R^h is hydrogen, $(C_1\text{-}6)$alkyl or phenyl;

R^i is hydrogen or phenyl optionally substituted by up to three groups selected from halogen, $(C_1\text{-}6)$-alkyl, or $(C_1\text{-}6)$alkoxy;

and

Y^1 is oxygen or NH;

for instance:

(a) acyloxyalkyl groups such as acetoxymethyl, isobutyryloxymethyl, pivaloyloxymethyl, benzoyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)ethyl, (1-aminoethyl)carbonyloxymethyl, 2-methoxyprop-2-ylcarbonyloxymethyl, phenylcarbonyloxymethyl and 4-methoxyphenyl-carbonyloxymethyl;

(b) alkoxy/cycloalkoxycarbonyloxyalkyl groups, such as ethoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, cyclohexyloxycarbonyloxymethyl, 1-methylcyclohexyloxycarbonyloxymethyl and α-ethoxycarbonyloxyethyl;

(c) dialkylaminoalkyl, especially di-loweralkylamino alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl;
(d) acetamido groups such as N,N-dimethylaminocarbonylmethyl, N,N-(2-hydroxyethyl)aminocarbonylmethyl;
(e) lactone groups such as phthalidyl and dimethoxyphthalidyl;
(f) (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl; and
(g) (2-methoxycarbonyl-*E*-but-2-en-yl)methyl.

Representative examples of pharmaceutically acceptable *in vivo* hydrolysable ester groups for R^{12} include:
(2-methoxycarbonyl-*E*-but-2-en-yl)methyl, isobutyryloxymethyl, 2-methoxyprop-2-ylcarbonyloxymethyl, phenylcarbonyloxymethyl, 4-methoxyphenyl-carbonyloxymethyl, t-butyloxycarbonyloxymethyl, cyclohexyloxy-carbonyloxymethyl, 1-methylcyclohexyloxycarbonyloxymethyl, N,N-dimethylaminocarbonylmethyl, and (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl.

It will be appreciated that when R^c is $C_{(1-3)}$alkyl, the carbon to which it is attached will be a chiral centre so that diastereoisomers may be formed. In the absence of further chiral centres, these will be enantiomers.. The present invention covers all such diastereosiomers and enatiomers, including mixtures thereof.

It will be appreciated that in some instances, compounds of the present invention may include a basic function such as an amino group as a substituent. Such basic functions may be used to form acid addition salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Such salts may be formed from inorganic and organic acids. Representative examples thereof include maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, taurocholic acid, benzenesulfonic, p-toluenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

It will be appreciated that in some instances, compounds of the present invention may include a carboxy group as a substituent. Such carboxy groups may be used to form salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Preferred salts include alkali metal salts such as the sodium and potassium salts.

When used herein, the term "alkyl" and similar terms such as "alkoxy" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

When used herein, the term "aryl" refers to, unless otherwise defined, a mono- or bicyclic aromatic ring system containing up to 10 carbon atoms in the ring system, for instance phenyl or naphthyl.

When used herein, the term "heteroaryl" refers to a mono- or bicyclic heteroaromatic ring system comprising up to four, preferably 1 or 2, heteroatoms each selected from oxygen, nitrogen and sulphur.

Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring.

When used herein, the terms "halogen" and "halo" include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

Particularly preferred compounds of formula (I) are

1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one;
1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one;
1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;
1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one; and
1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrimid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one; or a pharmaceutically acceptable salt thereof, in particular, the bitartrate salt

Since the compounds of the present invention, in particular compounds of formula (I), are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds of formula (I) may be used for preparing the more pure forms used in the pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are obtained in crystalline form.

When some of the compounds of this invention are allowed to crystallise or are re-crystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or re-crystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all polymorphic forms of the compounds of formula (I).

Compounds of the present invention are inhibitors of the enzyme lipoprotein associated phospholipase A_2 (Lp-PLA_2) and as such are expected to be of use in therapy, in particular in the treatment of atherosclerosis. In a further aspect therefore the present invention provides a compound of formula (I) for use in therapy.

The compounds of formula (I) are inhibitors of lysophosphatidylcholine production by Lp-PLA_2 and may therefore also have a general application in any disorder that involves endothelial dysfunction, for

example atherosclerosis, diabetes, hypertension, angina pectoris and after ischaemia and reperfusion. In addition, compounds of formula (I) may have a general application in any disorder that involves lipid oxidation in conjunction with enzyme activity, for example in addition to conditions such as atherosclerosis and diabetes, other conditions such as rheumatoid arthritis, stroke, inflammatory conditions of the brain such as Alzheimer's Disease, myocardial infarction, reperfusion injury, sepsis, and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia (see Psychopharmacology Bulletin, 31, 159-165, 1995).

Further applications include any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA_2. Examples of such disorders include psoriasis.

Accordingly, in a further aspect, the present invention provides for a method of treating a disease state associated with activity of the enzyme Lp-PLA_2 which method involves treating a patient in need thereof with a therapeutically effective amount of an inhibitor of the enzyme. The disease state may be associated with the increased involvement of monocytes, macrophages or lymphocytes; with the formation of lysophosphatidylcholine and oxidised free fatty acids; with lipid oxidation in conjunction with Lp PLA2 activity; or with endothelial dysfunction.

Compounds of the present invention may also be of use in treating the above mentioned disease states in combination with an anti-hyperlipidaemic, anti-atherosclerotic, anti-diabetic, anti-anginal, anti-inflammatory, or anti-hypertension agent or an agent for lowering Lp(a). Examples of the above include cholesterol synthesis inhibitors such as statins, anti-oxidants such as probucol, insulin sensitisers, calcium channel antagonists, and anti-inflammatory drugs such as NSAIDs. Examples of agents for lowering Lp(a) include the aminophosphonates described in WO 97/02037, WO 98/28310, WO 98/28311 and WO 98/28312 (Symphar SA and SmithKline Beecham).

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides, in a further aspect, a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

Suitable pharmaceutical compositions include those which are adapted for oral or parenteral administration or as a suppository.

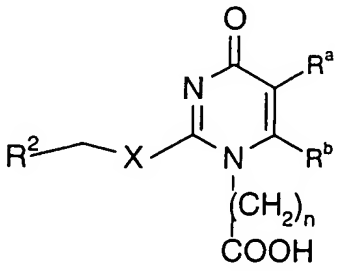
Suitable pharmaceutical compositions include those which are adapted for oral or parenteral administration or as a suppository. Compounds of formula (I) which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges. A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent. A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose. A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for

example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule. Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration. A typical suppository formulation comprises a compound of formula (I) which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule. Each dosage unit for oral administration contains preferably from 1 to 500 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I). The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg and 500 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I), the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

A compound of formula (I) may be prepared by a number of processes which include:

(a) reacting a compound of formula (II):



(II)

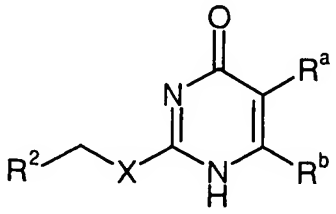
in which X, n, R^a, R^b and R^2 are as hereinbefore defined,
with a compound of formula (III):

$$R^5\text{-}R^4\text{-}CHR^cNHR^3$$

(III)

in which R^c, R^3, R^4 and R^5 are as hereinbefore defined; under amide forming conditions;

(b) reacting a compound of formula (IV):



(IV)

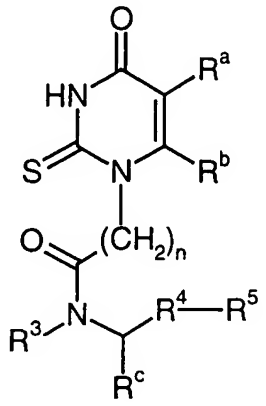
in which X, R^a, R^b and R^2 are as hereinbefore defined,

with a compound of formula (V):

$$R^5\text{-}R^4\text{-}CHR^cNR^3\text{-}CO\text{-}(CH_2)_n\text{-}L^1 \quad (V)$$

in which n, R^3, R^4 and R^5 are as hereinbefore defined, and L^1 is a leaving group such as halogen, for instance bromo or iodo,
in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane;

(c) when X is S, reacting a compound of formula (VI):



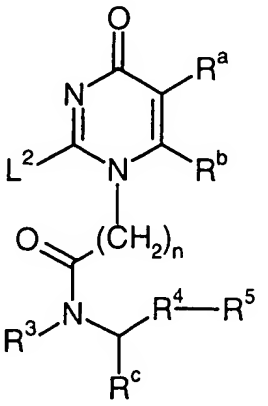
(VI)

in which n, R^a, R^b, R^c, R^3, R^4 and R^5 are as hereinbefore defined,
with a compound of formula (VII):

$$R^2\text{-}CH_2\text{-}L^1 \quad (VII)$$

in which R^2 and L^1 are as hereinbefore defined,
in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane;

(d) when X is O, reacting a compound of formula (VIII):



(VIII)

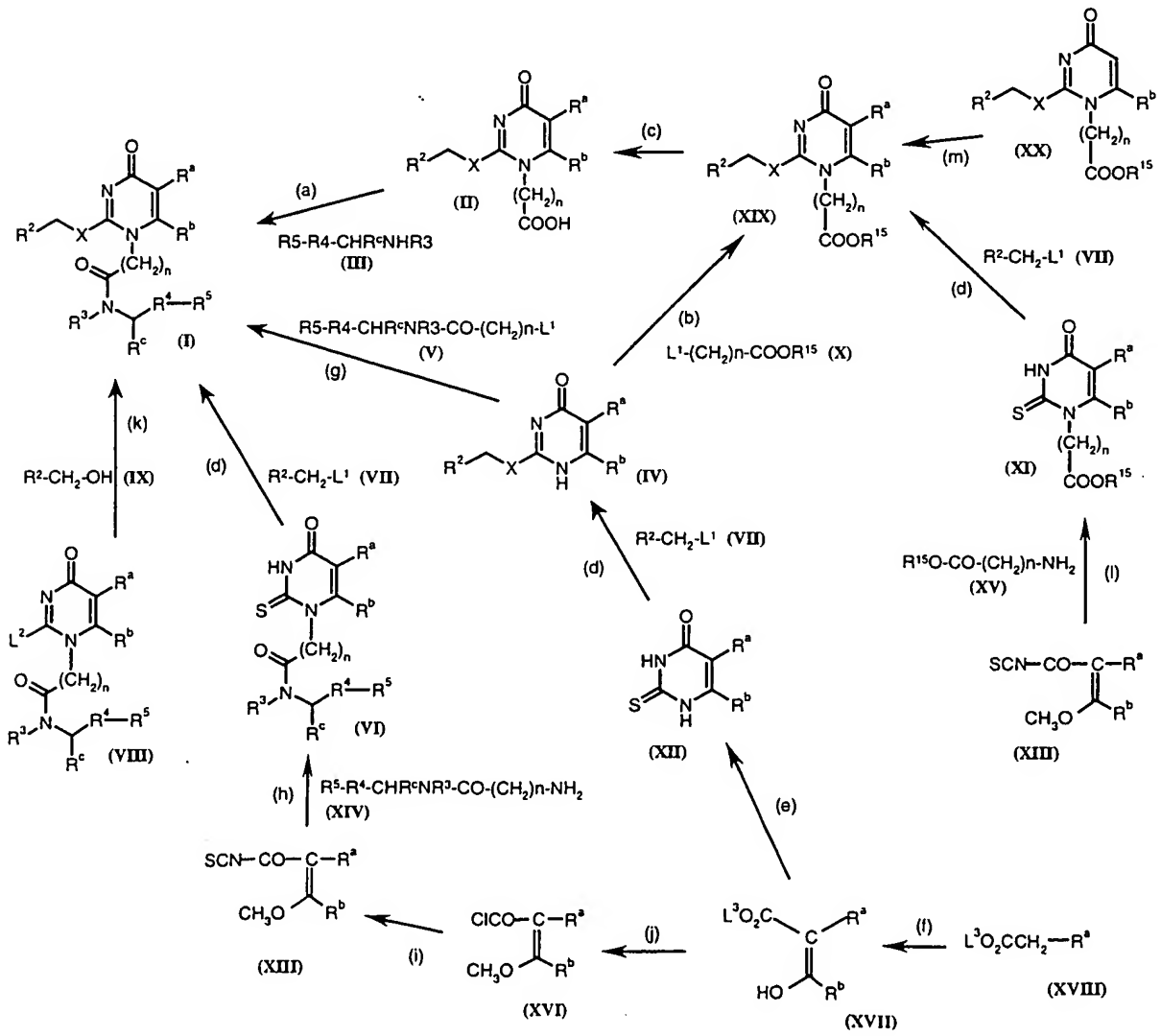
in which n, R^a, R^b, R^c, R^3, R^4 and R^5 are as hereinbefore defined, and L^2 is a leaving group such as halogen or alkylthio, for instance methylthio,
with a compound of formula (IX):

$$R^2\text{-}CH_2\text{-}OH \qquad (IX)$$

in which R^2 is as hereinbefore defined,
in the presence of a base such as 4-dimethylaminopyridine, in an inert solvent such as pyridine; or

(e) converting of compound of formula (I) to another compound of formula (I), by functional group modification, using methods well known to those skilled in the art, for example converting a compound of formula (I) in which R^a is aminoalkyl to a compound of formula (I) in which R^a is alkylcarbonylaminoalkyl, by reaction with an acylating agent, such as, for example, acetic anhydride.

Compounds of formulae (II), (IV), (VI) and (VIII) for use in the above processes may be prepared by processes illustrated in the following scheme I:



Scheme I

in which:

L^3 is a C(1-6)alkyl group, for instance methyl;
R^{15} is a $C_{(1-6)}$alkyl group, for instance ethyl or t-butyl and
L^1, L^2, R^a, R^b, R^2, R^3, R^4, R^5, n and X are as hereinbefore defined.

With reference to Scheme I:

Amide forming conditions for step (a) are well known in the art. Preferably, the acid of formula (II) is reacted with the amine of formula (III) in an inert solvent, such as dichloromethane, at ambient temperature and in the presence of an activating agent such as as O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate.

Alkylation conditions for step (b) include reaction in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethene.

Conditions for step (c) include hydrolysis, for instance using aqueous sodium hydroxide in a solvent such as dioxan or, when R^{15} is t-butyl, dealkylation with an acid such as trifluoroacetic acid in a solvent such as dichloromethane.

Conditions for step (d) include under thioether forming conditions. Advantageously, the reaction is carried out in the presence of a base such as sodium ethoxide or potassium carbonate, preferably in a solvent such as ethanol or dimethyl formamide, or a secondary or tertiary amine base such as di-isopropylethyl amine, in solvent such as dichloromethane.

In step (e), a compound of formula (XVII) is reacted with thiourea, in the presence of sodium ethoxide (preferably generated *in situ* from sodium and ethanol).

In step (f), a compound of formula (XVIII) is reacted with ethyl formate in the presence of a base such as sodium hydride or potassium isopropoxide.

In step (g), a compound of formula (IV) is reacted with a compound of formula (V) in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane

In step (h), a compound of formula (XIII) is reacted with a compound of formula (XIV) in a solvent such as dimethylformamide to form an intermediate thiourea, which is then treated with a base such as sodium methoxide.

In step (i), a compound of formula (XVI) is reacted with a metal thiocyanate, for example potassium thiocyanate, in a solvent such as acetonitrile.

In step (j), a compound of formula (XVII) is reacted with a methylating agent such as dimethyl sulphate in the presence of a base such as potassium carbonate, followed by hydrolysis of the intermediate ester in conventional manner e.g. by basic hydrolysis using sodium hydroxide to give the corresponding carboxylic acid which may then be converted into the acyl chloride, for instance by treatment with oxalyl chloride.

In step (k), a catalyst such as 4-dimethylaminopyridine, and in a solvent such as pyridine are used.

In step (l), a compound of formula (XIII) is reacted with a compound of formula (XV) in a solvent such as dimethylformamide to form an intermediate thiourea, which is then treated with a base such as sodium methoxide.

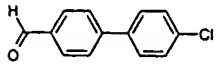
In step (m) a compound of formula (XX) is converted to a compound of formula (XIX), in which R^a is halogen, by treatment with N-halosuccinimide, for example N-chlorosuccinimide or N-bromo-succinimide, in a solvent such as carbon tetrachloride.

The present invention will now be illustrated by the following examples.

Examples

The structure and purity of the intermediates and examples was confirmed by 1H-NMR and (in nearly all cases) mass spectroscopy, even where not explicitly indicated below.

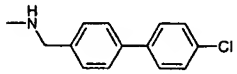
Intermediate A1 — 4-(4-Chlorophenyl)benzaldehyde



(a) A mixture of 4-formylbenzeneboronic acid (2.50g, 2 equiv), 4-chloroiodobenzene (1.98g, 1 equiv), tetrakis(triphenylphosphine)palladium(0) (0.50g, 0.05 equiv), aqueous sodium carbonate (18ml, 2M solution, 2 equiv) and dimethoxyethane (50ml) was stirred at reflux under argon overnight, then cooled and diluted with ethyl acetate. The mixture was filtered as necessary to remove inorganic residues, then the organic layer was washed successively with aqueous citric acid and brine, dried and evaporated. The crude product was purified by chromatography (silica, 5% ethyl acetate in hexane); product fractions were evaporated to a white solid (1.32g, 72%).

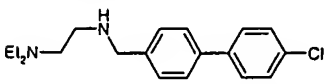
(b) A mixture of 4-chlorobenzeneboronic acid (19.4g, 1 equiv), 4-bromobenzaldehyde (22.9g, 1 equiv), palladium(II) acetate (1.4g, 0.05 equiv) aqueous sodium carbonate (30.3 g in 144ml solution, 2 equiv) and dimethoxyethane (500ml) was stirred at reflux under argon for 2.5h, then evaporated to low volume and diluted with dichloromethane. Workup continued as in (a) above to give identical material (25.2g, 94%). ^{1}H-NMR ($CDCl_3$) δ 10.05 (1H, s), 7.96 (2H, d), 7.73 (2H,d), 7.57 (2H, d), 7.46 (2H, d); MS (AP+) found (M+1) = 217, $C_{13}H_9{}^{35}ClO$ requires 216.

Intermediate A2 — N-Methyl-4-(4-chlorophenyl)benzylamine



A mixture of Intermediate A1 (3.5g, 1 equiv), methylamine (32.3ml of a 2M solution in THF, 4 equiv) and anhydrous magnesium sulphate (4.47g, 2 equiv) was stirred at room teperature for 16h, then filtered, the solid washed thoroughly with ethyl acetate, and the combined filtrates evaporated to a white solid (3.7g). This imine intermediate was suspended in ethanol (100ml), cooled in ice and sodium borohydride (0.61g, 1 equiv) added portionwise. The ice bath was removed, and the mixture stirred for 45min at room temperature then at 50°C for 1h. The solvent was removed in vacuo, water was added to the residue, and the product extracted into dichloromethane. Drying and evaporation of the solvent gave a white solid (3.56g). ^{1}H-NMR ($CDCl_3$) δ 7.51 (4H, d), 7.40 (4H, d), 3.79 (2H, s), 2.48 (3H, s); MS (APCI+) found (M+1) = 232, $C_{14}H_{14}{}^{35}ClN$ requires 231.

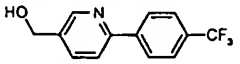
Intermediate A3 — N-(2-Diethylaminoethyl)-4-(4-chlorophenyl)benzylamine



A mixture of Intermediate A1 (55.0g), N,N-diethylethylenediamine (35.6ml), 4A molecular sieve (37g), and dichloromethane (1100ml) was reacted at room temperature under argon for 16h, with occasional agitation. The solid was filtered off and washed with dichloromethane, and the combined filtrates evaporated to a yellow foam (72.4g). This intermediate imine was reduced with sodium borohydride (8.7g) in ethanol (850ml) as described for Intermediate A2, yielding the title compound as a yellow oil

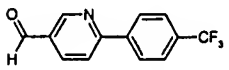
(72.7g). ^{1}H-NMR ($CDCl_3$) δ 1.70 (2H, t), 2.22 (6H, s), 2.33 (2H, t), 2.69 (2H, br. m), 3.83 (2H, s), 7.37-7.43 (4H, m), 7.52-7.56 (4H, m).

Intermediate A4 — 5-Hydroxymethyl-2-(4-trifluoromethylphenyl)pyridine



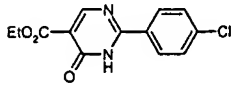
A solution of Intermediate A20 (4.63g) in dry dichloromethane (100ml) was cooled to -78°C under argon, then DIBAL-H (26.7ml, 1.5M solution in toluene) was added dropwise over 20min. Stirring was continued for 40min at -78°C, then 2M hydrochloric acid (52ml) was added dropwise over 15min. The solution was allowed to warm slowly to room temperature, then the organic layer was separated, washed with water, dried and evaporated. Chromatography (silica, 1:1 ethyl acetate/hexane) gave the product as a white solid (3.03g, 75%). ^{1}H-NMR ($CDCl_3$) δ 1.85 (1H,t), 4.81 (2H,d), 7.75 (2H,m), 7.83 (1H,dd), 8.11 (1H,d), 8.72 (1H,m); MS(APCI+) found (M+1)=254, $C_{13}H_{10}F_3NO$ requires 253.

Intermediate A5 — 5-Formyl-2-(4-trifluoromethylphenyl)pyridine



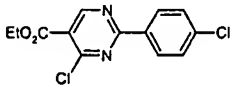
Activated manganese dioxide (3.19g) was added to a solution of Intermediate A4 (0.75g) in dichloromethane (50ml) and stirred at room temperature for 16h. The solids were filtered off and the filtrate evaporated to a pale yellow solid (0.57g). ^{1}H-NMR ($CDCl_3$) δ 7.7 (2H,d), 7.96 (1H,d), 8.21 (2H,d), 8.27 (1H,dd), 9.17 (1H,d), 10.19 (1H,s); MS(APCI+) found (M+1)=252, $C_{13}H_8F_3NO$ requires 251.

Intermediate A6 — Ethyl 2-(4-chlorophenyl)-4-oxopyrimidine-5-carboxylate



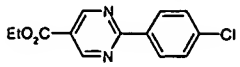
Sodium ethoxide (11.12 ml, 2 equiv) as a 21% w/v solution in ethanol was added dropwise to a suspension of diethyl ethoxymalonate (3.03 ml, 1 equiv) and 4-chlorobenzamidine hydrochloride (4.23 g, 1 equiv) in ethanol (30 ml), then the mixture was heated to reflux for 4 hours. After cooling, the solvent was removed in vacuo and the residue was triturated with ether. The solid was filtered off, then resuspended in water and acidified to pH 2. The product was filtered off, washed with water and dried; yield 2.94 g. ^{1}H-NMR (d_6-DMSO) δ 1.29 (3H,t), 4.26 (2H,q), 7.65 (2H,m), 8.18 (2H,m), 8.65 (1H,s); MS (APCI-) found (M-1) = 277/279; $C_{13}H_{11}ClN_2O_3$ requires 278/280.

Intermediate A7 — Ethyl 2-(4-chlorophenyl)-4-chloropyrimidine-5-carboxylate



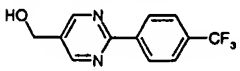
Oxalyl chloride (0.31 ml, 2 equiv) was added to Intermediate A6 (0.49 g) in dichloromethane (20 ml) with ice cooling, then the mixture was stirred for 3 hours with warming to room temperature. Evaporation of the volatile components gave the product as a white solid (2.94 g). ^{1}H-NMR ($CDCl_3$) δ 1.44 (3H,t), 4.48 (2H,q), 7.50 (2H,m), 8.45 (2H,m), 9.17 (1H,s); MS (APCI+) found (M+1) = 297; $C_{13}H_{10}Cl_2N_2O_2$ requires 296.

Intermediate A8 — Ethyl 2-(4-chlorophenyl)pyrimidine-5-carboxylate



A mixture of Intermediate A7 (6.8 g, 1 equiv), zinc powder (1.79 g, 1.2 equiv), acetic acid (1.57 ml, 1.2 equiv) and THF (100 ml) was stirred at 60°C under argon for 18 hours, then a further portion of acetic acid (1 ml) and zinc (1.0 g) was added, and the reaction allowed to continue for a further 24 hours. The solvent was removed in vacuo, the residue was taken up in a mixture of dichloromethane and methanol, and undissolved zinc powder was removed by filtration. After evaporation of the solvent, the product crystallised from ethanol; yield 2.02 g. ^{1}H-NMR ($CDCl_3$) δ 1.44 (3H,t), 4.46 (2H,q), 7.48 (2H,m), 8.48 (2H,m), 9.30 (2H,s); MS (APCI+) found (M+1) = 263; $C_{13}H_{11}ClN_2O_2$ requires 262.

Intermediate A9 — 5-Hydroxymethyl-2-(4-trifluoromethylphenyl)pyrimidine

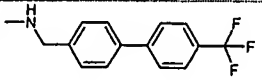
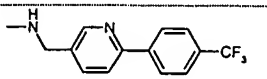


Intermediate A41 (0.96g) was hydrogenated over 10% palladium on charcoal (96 mg) in a mixture of triethylamine (2 ml) and ethanol (20 ml) for 90 mins at 1 atmosphere pressure. The catalyst was removed by filtration, the solvent was evaporated, and the residue was taken up in ethyl acetate and washed successively with aq. ammonium chloride and aq. sodium bicarbonate. Drying and evaporation gave the title compound (0.77 g). ^{1}H-NMR ($CDCl_3$) δ 4.82 (2H,s), 7.75 (2H,m), 8.57 (2H,m), 8.85 (2H,s); MS (APCI+) found (M+1) = 255; $C_{12}H_9F_3N_2O$ requires 254.

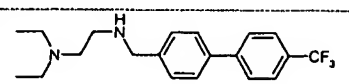
The following intermediates were made by the method of Intermediate A1:

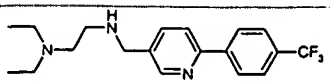
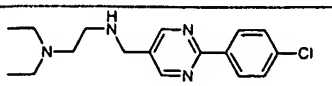
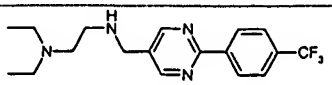
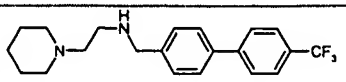
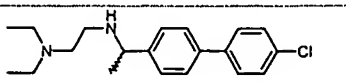
No.	Precursors	Name
A20	methyl 6-chloronicotinate, 4-trifluoromethylbenzeneboronic acid	Methyl 6-(4-trifluoromethylphenyl)nicotinate
A21	4-bromobenzaldehyde, 4-trifluoromethylbenzeneboronic acid	4-(4-Trifluoromethylphenyl)benzaldehyde
A22	4-bromoacetophenone, 4-chlorobenzeneboronic acid	4-acetyl-4'-chlorobiphenyl

The following intermediates were made by the method of Intermediate A2:

No.	Precursor	Structure	Name
A25	Int. A21		N-Methyl-4-(4-trifluoromethylphenyl)benzylamine
A26	Int. A5		N-methyl-2-(4- trifluoromethyl phenyl)pyrid-5-yl-methylamine

The following intermediates were made by the method of Intermediate A3:

No.	Precursor	Structure	Name
A30	Int. A21		N-(2-(diethylamino)ethyl)-4-(4-trifluoro-methylphenyl)benzylamine

A31	Int. A5		N-(2-(diethylamino)ethyl)-2-(4-trifluoro-methylphenyl)pyrid-5-ylmethylamine
A32	Int. A50		N-(2-(diethylamino)ethyl)-2-(4-chloro-phenyl)pyrimid-5-ylmethylamine
A33	Int. A51		N-(2-(diethylamino)ethyl)-2-(4-trifluoro-methylphenyl)pyrimid-5-ylmethylamine
A34	Int. A21		N-(2-(1-piperidino)ethyl)-4-(4-trifluoro-methylphenyl)benzylamine
A35	Int. A22		(±)-N-(2-(diethylamino)ethyl)-1-(4-(4-chlorophenyl)phenyl)ethylamine

The following intermediates were made by the method of Intermediate A4:

No.	Precursor	Name
A40	Int. A8	5-Hydroxymethyl-2-(4-chlorophenyl)pyrimidine
A41	Int. A53	4-chloro-5-hydroxymethyl-2-(4-trifluoromethylphenyl)pyrimidine

The following intermediates were made by the method of Intermediate A5:

No.	Precursor	Name
A50	Int. A40	5-Formyl-2-(4-chlorophenyl)pyrimidine
A51	Int. A9	5-Formyl-2-(4-trifluoromethylphenyl)pyrimidine

The following intermediate was made by the method of Intermediate A6:

No.	Precursors	Name
A52	diethyl ethoxymalonate, 4-trifluoromethylbenzamidine.HCl	Ethyl 2-(4-trifluoromethylphenyl)-4-oxopyrimidine-5-carboxylate

The following intermediate was made by the method of Intermediate A7:

No.	Precursor	Name
A53	Int. A52	Ethyl 2-(4-trifluoromethylphenyl)-4-chloropyrimidine-5-carboxylate

5

The following compounds are commercially available:
Intermediate B1, 2-thiouracil; Intermediate B2, 5-methyl-2-thiouracil ; Intermediate B3, 5-ethyl-2-thiouracil; Intermediate B4, 5-propyl-2-thiouracil; Intermediate B5, 5,6-dimethyl-2-thiouracil; Intermediate B6, 5-carbethoxy-2-thiouracil; Intermediate B7, 5,6-trimethylene-2-thiouracil; Intermediate B8, 5,6-tetramethylene-2-thiouracil; Intermediate B9, 5-methoxy-2-thiouracil

Intermediate B10 — 5-(2-hydroxyethyl)-2-thiouracil

A solution of ethyl formate (33.1 ml, 2.1 equiv) and γ-butyrolactone (15 ml, 1 equiv) in ether (400 ml) was added dropwise with stirring to a solution of potassium t-butoxide (52.5 g, 2.4 equiv) in tetrahydrofuran (400 ml). The mixture was allowed to warm to room temperature, and stirred overnight. The solvent was removed in vacuo, 2-propanol (600 ml) and thiourea (29.7 g, 2 equiv) were added, and the mixture was heated to reflux for 5h. After cooling to room temperature, the precipitate was filtered off, dissolved in water (500 ml), and washed twice with ether. The aqueous solution was acidified to pH5.5 with acetic acid, and the resulting precipitate was filtered off, washed thoroughly with water, and dried in vacuo; yield 23.85 g. ^{1}H-NMR (d_6-DMSO) δ 2.36 (2H,t), 3.47 (2H,m), 4.57 (1H,m), 7.24 (1H,s), 12.2 & 12.4 (each 1H, br s); MS (APCI-) found (M-H) = 171; $C_6H_8N_2O_2S$ requires 172.

The following intermediates were prepared by the method of Intermediate B10

No.	Ester precursor	Name
B11	monoethyl succinate	5-carboxymethyl-2-thiouracil
B12	ethyl ethoxyacetate	5-ethoxy-2-thiouracil
B13	ethyl (methylthio)acetate	5-methylthio-2-thiouracil

Intermediate B20 — 2-(4-fluorobenzylthio)-5-methylpyrimidin-4-one

A mixture of Intermediate B2 (9.45 g, 1 equiv), 4-fluorobenzyl chloride (7.96 ml, 1 equiv), potassium carbonate (18.4 g, 2 equiv) and dimethyl formamide (100 ml) was stirred at 90°C under argon for 16h. The DMF was removed in vacuo, water was added, and the product was extracted into ethyl acetate. The organic layer was dried and evaporated, and the residue was triturated with petroleum ether to obtain the title compound as a white solid (8.76 g). ^{1}H-NMR ($CDCl_3$) δ 2.02 (3H,s), 4.38 (2H,s), 6.97 (2H,m), 7.35 (2H,m), 7.74 (1H,s); MS (APCI+) found (M+1) = 251; $C_{12}H_{11}FN_2OS$ requires 250.

The following intermediates were prepared by the method of Intermediate B20:

No.	Precursor	Name
B21	Int. B1	2-(4-fluorobenzylthio)pyrimidin-4-one
B22	Int. B3	2-(4-fluorobenzylthio)-5-ethylpyrimidin-4-one
B23	Int. B4	2-(4-fluorobenzylthio)-5-propylpyrimidin-4-one
B24	Int. B6	2-(4-fluorobenzylthio)-5-ethoxycarbonylpyrimidin-4-one
B25	Int. B10	2-(4-fluorobenzylthio)-5-(2-hydroxyethyl)pyrimidin-4-one
B26	Int. B5	2-(4-fluorobenzylthio)-5,6-dimethylpyrimidin-4-one

B27	Int. B7	2-(4-fluorobenzylthio)-5,6-trimethylenepyrimidin-4-one
B28	Int. B8	2-(4-fluorobenzylthio)-5,6-tetramethylenepyrimidin-4-one
B29	Int. B9	2-(4-fluorobenzylthio)-5-methoxypyrimidin-4-one
B30	Int. B12	2-(4-fluorobenzylthio)-5-ethoxypyrimidin-4-one
B31	Int. B13	2-(4-fluorobenzylthio)-5-methylthiopyrimidin-4-one

Intermediate B37 — 2-(4-fluorobenzylthio)-5-hydroxymethylpyrimidin-4-one

Borane-tetrahydrofuran complex (143 ml, 2.2 equiv, 1.0M in THF) was added dropwise to an ice-cooled solution of Intermediate B24 (20 g, 1 equiv) in dry THF (700 ml) under argon with stirring. After a further 30 min at 0°C, the mixture was allowed to warm to room temperature and stirring continued overnight. The solvent was evaporated, 50% aqueous acetic acid (500 ml) was added with stirring, and the mixture was evaporated to dryness. The residue was digested with hot water (500 ml) for 5 min, then the solid was filtered off. Both this solid and the filtrate were extracted with dichloromethane, and the organic extracts were combined and purified by chromatography (silica, 2-8% methanol in dichloromethane). Product fractions were evaporated to a white solid (6.14 g). ^{1}H-NMR (d_6-DMSO) δ 4.25 (2H,S), 4.39 (2H,S), 7.14 (2H,t), 7.45 (2H,m), 7.82 (1H, br s); MS (APCI+) found (M+1) = 267; $C_{12}H_{11}FN_2O_2S$ requires 266.

Intermediate B38 — 2-(4-fluorobenzylthio)-5-isopropoxycarbonylmethylpyrimidin-4-one

A mixture of Intermediate B11 (2.60 g, 1 equiv), 4-fluorobenzyl bromide (1.74 ml, 1 equiv) and 2-propanol (50 ml) was stirred at reflux for 3h, then concentrated to a slurry in vacuo and diluted with ether. The solid was filtered off, washed with ether and dried; yield 2.87 g. ^{1}H-NMR (d_6-DMSO) δ 1.17 (6H,d), 3.31 (2H,s), 4.40 (2H,s), 4.89 (1H,m), 7.14 (2H,t), 7.45 (2H,m), 7.84 (1H,s); MS (APCI+) found (M+1) = 267; $C_{12}H_{11}FN_2O_2S$ requires 266.

Intermediate B40 — 1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-methylpyrimidin-4-one

A mixture of Intermediate B20 (6.30 g, 1 equiv), t-butyl iodoacetate (6.1 g, 1 equiv), diisopropylethylamine (5.27 ml, 1.2 equiv) and dichloromethane (100 ml) was stirred at ambient temperature under argon for 16h, then the solution was washed with aq. ammonium chloride and aq. sodium bicarbonate, dried and evaporated. Chromatography (silica, ethyl acetate + 0.5% v/v aq. ammonia) followed by crystallisation from ethyl acetate gave the title compound as a white solid (3.36 g). ^{1}H-NMR ($CDCl_3$) δ 1.44 (9H,s), 2.01 (3H,d), 4.36 (2H,s), 4.51 (2H,s), 6.98 (3H,m), 7.36 (2H,m); MS (APCI+) found (M+1) = 365; $C_{18}H_{21}FN_2O_3S$ requires 364.

The following intermediates were prepared by the method of Intermediate B40:

No.	Precursor	Name
B41	Int. B21	1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)pyrimidin-4-one
B42	Int. B22	1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-ethylpyrimidin-4-one
B43	Int. B23	1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-propylpyrimidin-4-one

B44	Int. B24	1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-ethoxycarbonyl-pyrimidin-4-one
B45	Int. B38	1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-isopropoxycarbonylmethylpyrimidin-4-one
B46	Int. B37	1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-hydroxymethyl-pyrimidin-4-one
B47	Int. B25	1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-(2-hydroxyethyl)-pyrimidin-4-one
B48	Int. B26	1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5,6-dimethyl-pyrimidin-4-one
B49	Int. B27	1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5,6-trimethylene-pyrimidin-4-one
B50	Int. B28	1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5,6-tetramethylene-pyrimidin-4-one
B51	Int. B29	1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-methoxy-pyrimidin-4-one
B52	Int. B30	1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-ethoxypyrimidin-4-one
B53	Int. B31	1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-methylthio-pyrimidin-4-one

Intermediate B56 — 1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-chloropyrimidin-4-one

A mixture of Intermediate B41 (7.45 g, 1 equiv), N-chlorosuccinimide (2.84 g, 1 equiv) and carbon tetrachloride (150 ml) was stirred at reflux under argon for 2h, then the solution was evaporated. Chromatography (silica, ethyl acetate) followed by trituration with ether gave the title compound as a white solid (4.45 g). ^{1}H-NMR ($CDCl_3$) δ 1.45 (9H,s), 4.40 (2H,s), 4.50 (2H,s), 6.99 (2H,m), 7.35 (2H,m), 7.40 (1H,s); MS (APCI+) found (M+1) = 385/387; $C_{17}H_{18}ClFN_2O_3S$ requires 384/386.

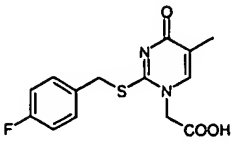
Intermediate B57 — 1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-bromopyrimidin-4-one

Prepared as Intermediate B56, but using N-bromosuccinimide in place of N-chlorosuccinimide. ^{1}H-NMR ($CDCl_3$) δ 1.45 (9H,s), 4.40 (2H,s), 4.49 (2H,s), 6.99 (2H,m), 7.35 (2H,m), 7.53 (1H,s); MS (APCI+) found (M+1) = 429/431; $C_{17}H_{18}BrFN_2O_3S$ requires 428/430.

Intermediate B58 — 1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-methylsulfinyl-pyrimidin-4-one

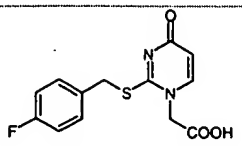
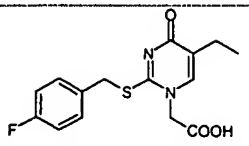
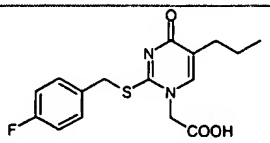
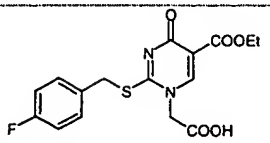
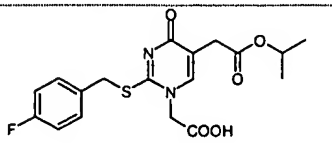
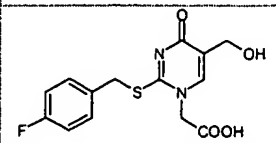
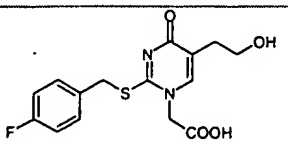
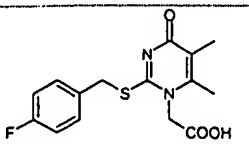
m-Chloroperbenzoic acid (0.93 g) was added to an ice-cooled slurry of Intermediate B53 (1.50 g) in dichloromethane (20 ml). The resulting solution was allowed to warm to room temperature and stirred for 30 min, then washed with aq. sodium bicarbonate. Chromatography (silica, 3-8% methanol in ethyl acetate) gave the title compound as a white solid (1.15 g). ^{1}H-NMR ($CDCl_3$) δ 1.46 (9H,s), 2.94 (3H,s), 4.51 (4H,m), 7.01 (2H,m), 7.37 (2H,m), 7.60 (1H,s); MS (APCI+) found (M+1) = 413; $C_{18}H_{21}FN_2O_4S_2$ requires 412.

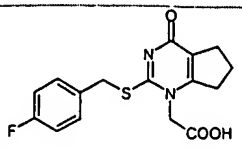
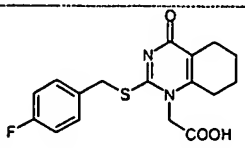
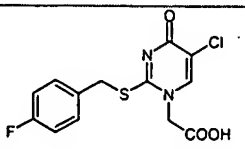
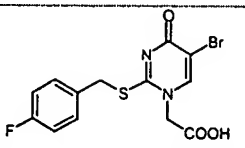
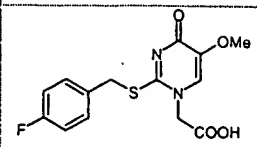
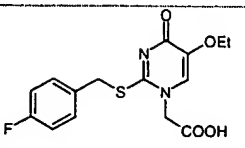
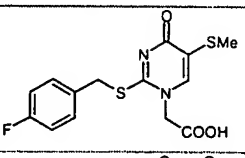
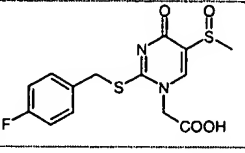
Intermediate B60 — 1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-methylpyrimidin-4-one



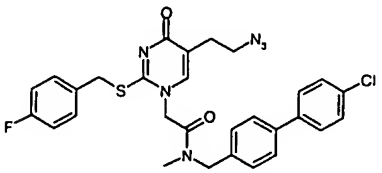
Intermediate B40 (3.88 g) was added to solution of trifluoroacetic acid (10 ml) in dichloromethane (20 ml) under argon, and stirred overnight at room temperature. Evaporation of the solvent and trituration with ether gave the title compound as a white solid (3.04 g). ^{1}H-NMR (d_6-DMSO) δ 1.81 (3H,d), 4.42 (2H,s), 4.66 (2H,s), 7.14 (2H,m), 7.47 (2H,m), 7.63 (1H,m); MS (APCI+) found (M+1) = 309; $C_{14}H_{13}FN_2O_3S$ requires 308.

The following intermediates were prepared by the method of Intermediate B60:

No.	Precursor	Structure	Name
B61	Int. B41		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-pyrimidin-4-one
B62	Int. B42		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-ethylpyrimidin-4-one
B63	Int. B43		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-propylpyrimidin-4-one
B64	Int. B44		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-ethoxycarbonylpyrimidin-4-one
B65	Int. B45		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-isopropoxycarbonylmethylpyrimidin-4-one
B66	Int. B46		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-hydroxymethylpyrimidin-4-one
B67	Int. B47		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-(2-hydroxyethyl)pyrimidin-4-one
B68	Int. B48		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5,6-dimethylpyrimidin-4-one

B69	Int. B49		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5,6-trimethylenepyrimidin-4-one
B70	Int. B50		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5,6-tetramethylenepyrimidin-4-one
B71	Int. B56		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-chloropyrimidin-4-one
B72	Int. B57		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-bromopyrimidin-4-one
B73	Int. B51		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-methoxypyrimidin-4-one
B74	Int. B52		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-ethoxypyrimidin-4-one
B75	Int. B53		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-methylthiopyrimidin-4-one
B76	Int. B58		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-methylsulfinylpyrimidin-4-one

Intermediate B80 — 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-azidoethyl)pyrimidin-4-one



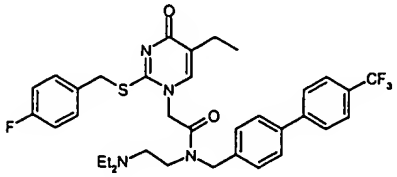
A mixture of Example 39 (1.88 g, 1 equiv), methanesulfonic anhydride (0.713 g, 1.2 equiv), triethylamine (0.665 ml) and dichloromethane (20 ml) was stirred at 0°C for 4h. The solution was washed with water, dried and evaporated to a pale foam (2.4 g). This was dissolved in dimethylformamide (20 ml), sodium azide (0.266 g, 1.2 equiv) was added, and the mixture was stirred under argon at room temperature overnight. The solvent was evaporated, the residue was partitioned between water and dichloromethane, and the organic layer was dried and evaporated. Chromatography (silica, ethyl acetate) gave the title compound as a white solid. ^{1}H-NMR ($CDCl_3$) δ 2.66 (2H,m), 2.88

(3H, s), 3.60(2H, m), 4.46-4.64 (6H, m), 6.84-7.50 (12H, m), 8.02 (1H,s); MS (APCI+) found (M+1) = 577/579; $C_{29}H_{26}ClFN_6O_2S$ requires 576/578.

The following compound was prepared by the method of Intermediate B80

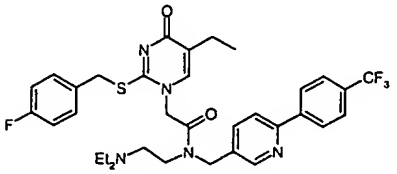
No.	Precursor	Name
B81	Example 42	1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-azidoethyl)pyrimidin-4-one

Example 1 — 1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one bitartrate



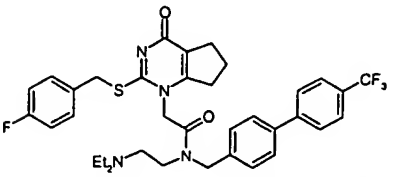
A mixture of Intermediate A30 (0.403 g, 1 equiv), Intermediate B62 (0.371 g, 1 equiv), HATU (0.426 g, 1.2 equiv), diisopropylethylamine (0.482 ml, 2.4 equiv) and dichloromethane (15 ml) was stirred at room temperature overnight, then washed with aqueous ammonium chloride and aqueous sodium bicarbonate. The organic layer was dried and evaporated, and the product purified by chromatography (silica, 5% methanol in dichloromethane). Product fractions were evaporated to a white foam (0.627 g). This free base (0.612 g) was dissolved in methanol (10 ml), tartaric acid (0.14 g) was added, the mixture was stirred for 5 mins then evaporated. Trituration with ether gave the bitartrate salt as a white solid (0.622 g). ^{1}H-NMR (d_6-DMSO, ca 1:1 rotamer mixture) δ 0.96 (3H,m), 1.07 (6H,m), 2.27 (2H,m), 2.59 (2H,m), 2.84 (2H,m), 3.37/3.50 (4H,m), 4.26 (2H,s), 4.39/4.43 (2H,2x s), 4,64/4.72 (2H,2x s), 4,94/5.09 (2H,2x s), 7.11/7.14 (2H,2x m), 7.36-7.49 (5H, m), 7.63/7.72 (2H,2x d), 7.84 (4H,m); MS (APCI+) found (M+1) = 602; $C_{32}H_{29}ClFN_5O_2S$ requires 601.

Example 2 — 1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one bitartrate



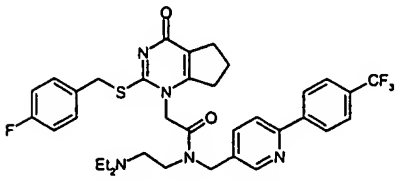
Prepared from intermediates A31 and B62 by the method of Example 1. ^{1}H-NMR (d_6-DMSO, ca 2:1 rotamer mixture) δ 0.93 (6H,m), 1.08 (3H,m), 2.27 (2H,m), 2.66 (4H,m), 3.39/3.45 (4H,m), 4.21 (2H,s), 4.39/4.42 (2H,2x s), 4,66/4.77 (2H,2x s), 4,97/5.10 (2H,2x s), 7.09/7.12 (2H,2x t), 7.42/7.49 (2H,2x t), 7.79/7.86 (1H,2x dd), 7.87 (2H,d), 7.97/8.06 (1H,2x dd), 8.28 (2H,d), 8.62/8.71 (2H,2x s); MS (APCI+) found (M+1) = 656; $C_{33}H_{37}F_4N_5O_2S$ requires 655.

Example 3 — 1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one bitartrate



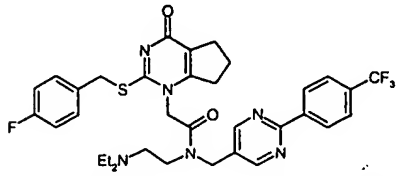
Prepared from intermediates A30 and B69 by the method of Example 1. ^{1}H-NMR (d_6-DMSO, ca 1:1 rotamer mixture) δ 0.92/0.99 (6H,t), 1.99 (2H,m), 2.59 (4H,m), 2.68/2.74 (4H,m), 3.36 (2H,m), 4.21 (2H,s), 4.37/4.44 (2H,2x s), 4,63/4.74 (2H,2x s), 4,89/5.13 (2H,2x s), 7.08/7.14 (2H,2x m), 7.36-7.50 (5H, m), 7.64/7.70 (2H,2x d), 7.83 (4H,m); MS (APCI+) found (M+1) = 667; $C_{36}H_{38}F_4N_4O_2S$ requires 666.

Example 4 — 1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one bitartrate



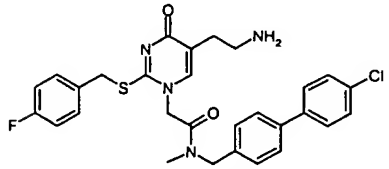
Prepared from intermediates A31 and B69 by the method of Example 1. ^{1}H-NMR (d_6-DMSO, ca 3:1 rotamer mixture) δ 0.92/0.98 (6H,t), 1.99 (2H,m), 2.59 (4H,m), 2.68/2.75 (4H,m), 3.41 (2H,m), 4.22 (2H,s), 4.37/4.42 (2H,2x s), 4,66/4.79 (2H,2x s), 4,93/5.13 (2H,2x s), 7.07/7.12 (2H,2x t), 7.39/7.47 (2H,2x t), 7.77/7.86 (1H,2x dd), 7.87 (2H,d), 7.98/8.05 (1H,2x dd), 8.28 (2H,d), 8.61/8.69 (2H,2x s); MS (APCI+) found (M+1) = 668; $C_{35}H_{37}F_4N_5O_2S$ requires 667.

Example 5 — 1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrimid-5-ylmethyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one bitartrate



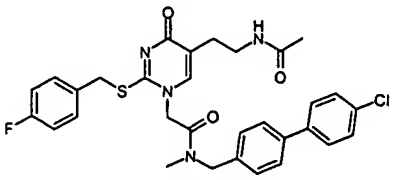
Prepared from intermediates A33 and B69 by the method of Example 1. ^{1}H-NMR (d_6-DMSO, ca 3:1 rotamer mixture) δ 0.92/1.09 (6H,t), 1.96 (2H,m), 2.60 (4H,m), 2.75 (4H,m), 3.48 (2H,m), 4.23 (2H,s), 4.38/4.40 (2H,2x s), 4,65/4.81 (2H,2x s), 4,97/5.11 (2H,2x s), 7.07/7.10 (2H,2x t), 7.38/7.44 (2H,2x t), 7.91 (2H,d), 8.57 (2H,d), 8.84/8.93 (2H,2x s); MS (APCI+) found (M+1) = 669; $C_{34}H_{36}F_4N_6O_2S$ requires 668.

Example 6 — 1-(N-Methyl-N-(2-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluoro-benzyl)thio-5-(2-aminoethyl)pyrimidin-4-one hydrochloride



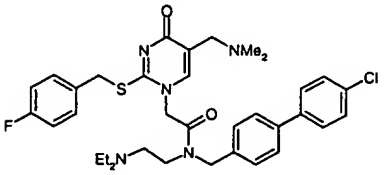
A solution of Intermediate B80 (0.228 g) in ethanol (20 ml) was hydrogenated over 10% palladium on charcoal (0.09 g) at atmospheric pressure for 2 days. The catalyst was filtered off, the solvent was removed in vacuo, and the resulting oil was purified by chromatography (silica, 10% methanolic ammonia in dichloromethane). The free base was dissolved in dichloromethane (5 ml), and an equimolar quantity of hydrogen chloride in ether added. The solvent was removed in vacuo, and the residue triturated with ether; yield 0.132 g). ^{1}H-NMR (d_6-DMSO, ca 2:1 rotamer mixture) δ 2.58 (2H,m), 2.87/2.99 (3H,2x s), 2.99 (2H,m), 4.40/4.45 (2H,2x s), 4.57/4.66 (2H,2x s), 4.97/5.00 (2H,2x s), 7.16 (2H,m), 7.33/7.38 (2H,2x d), 7.4-7.7 (9H,m), 8.0 (2H,br m); MS (APCI+) found (M+1) = 551/553; $C_{29}H_{28}ClFN_4O_2S$ requires 550/552.

Example 7 — 1-(N-Methyl-N-(2-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-acetamidoethyl)pyrimidin-4-one



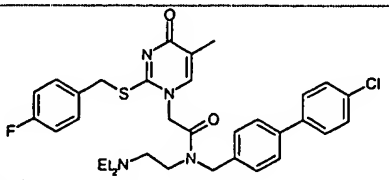
A solution of Example 6 (0.173 g, 1 equiv), acetic anhydride (0.033 ml, 1.1 equiv) and diisopropylamine (0.066 ml, 1.2 equiv) in dichloromethane (10 ml) was stirred at room temperature overnight. The solution was washed with aq. ammonium chloride and aq. sodium bicarbonate, then the organic layer was dried and evaporated. The residue was triturated with ether to obtain the title compound as a white solid (0.156 g). ^{1}H-NMR ($CDCl_3$, ca 2:1 rotamer mixture) δ 1.96 (3H,s), 2.64 (2H,m), 2.96/3.10 (3H, 2x s), 3.49 (2H,m), 4.46-4.64 (6H,m), 6.77 (1H,br t), 6.97-7.16 (3H,m), 7.26-7.49 (10H,m); MS (APCI+) found (M+1) = 593/595; $C_{31}H_{30}ClFN_4O_3S$ requires 592/594.

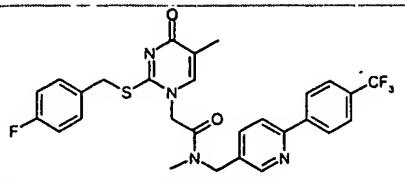
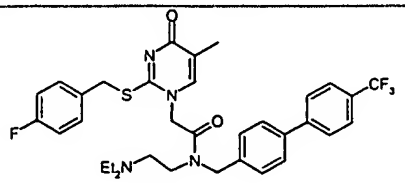
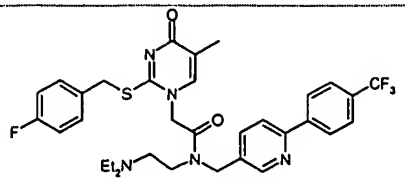
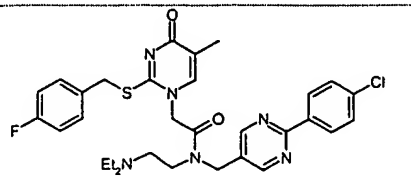
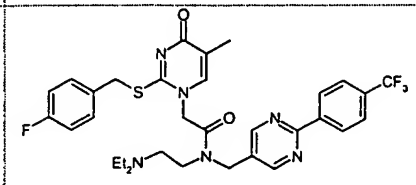
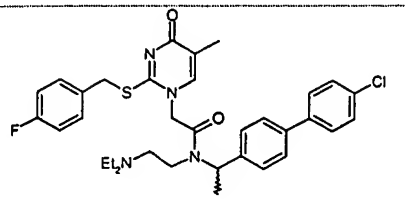
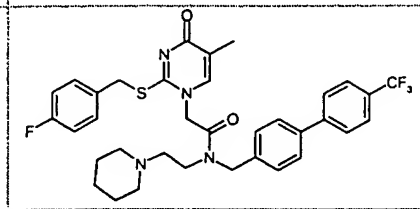
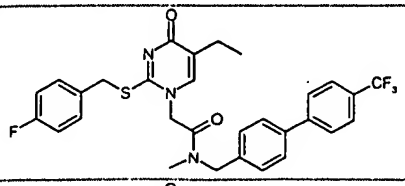
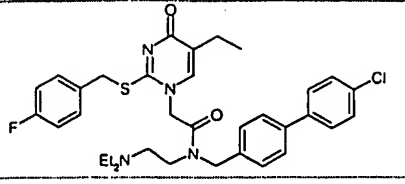
Example 8 — 1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(dimethylaminomethyl)pyrimidin-4-one

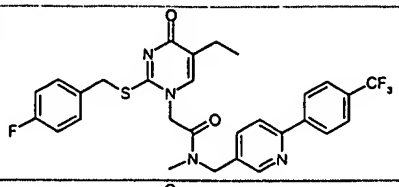
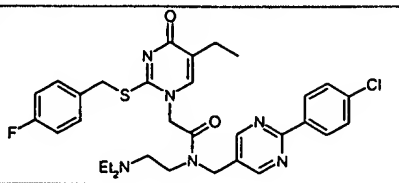
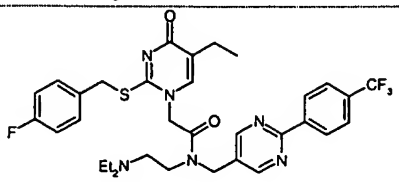
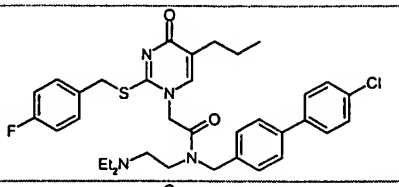
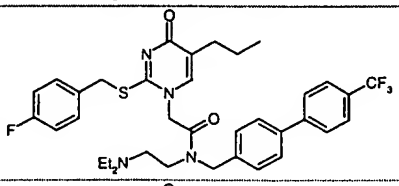
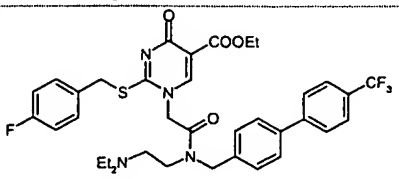
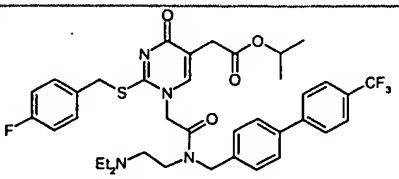
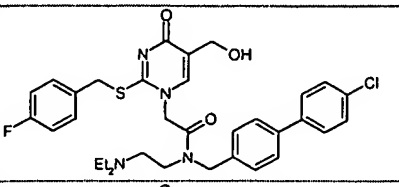
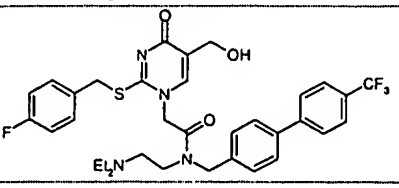


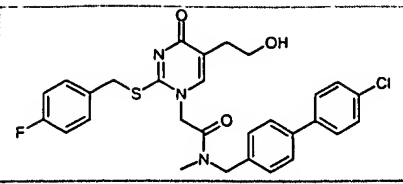
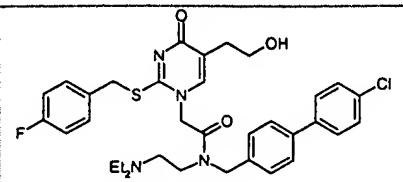
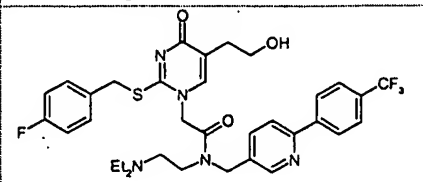
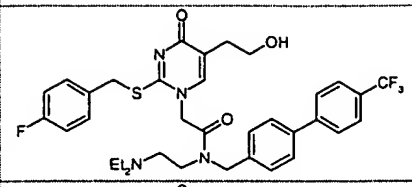
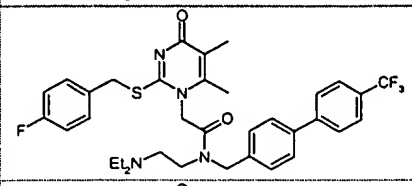
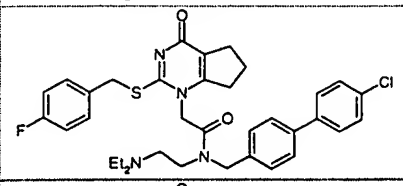
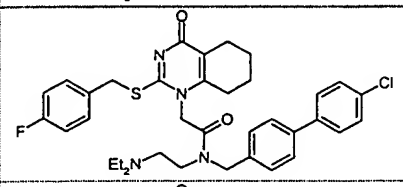
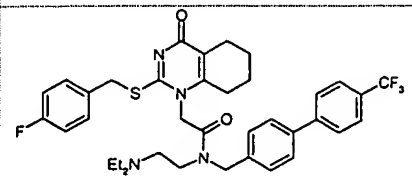
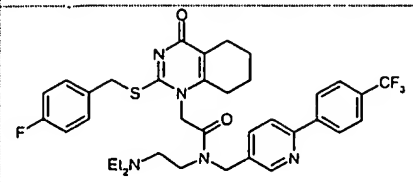
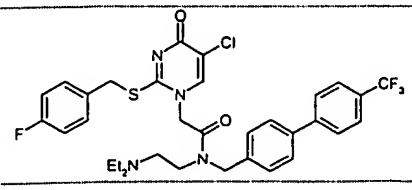
Methanesulfonic anhydride (0.134 g, 1.2 equiv) was added to a solution of Example 38 (0.40 g, 1 equiv) and triethylamine (0.124 ml, 1.4 equiv) in dichloromethane (5 ml) at 0°C, then stirred at this temperature for 4 hours. The mixture was washed with water, dried and evaporated to yield the mesylate as a pale yellow solid. This was dissolved in a 2M solution of dimethylamine in THF (10 ml) and stirred at room temperature for 16 hours. The solvent and excess dimethylamine was removed in vacuo, and the product was purified by chromatography (silica, 5-20% methanol in ethyl acetate, then 1-10% methanolic ammonia in dichloromethane) to obtain the title compound. ^{1}H-NMR ($CDCl_3$) δ 0.98 (6H,t), 2.28/2.30 (each 3H,s), 2.46-2.65 (6H,m), 3.26/3.56 (2H,2x t), 3.33/3.36 (2H,2x s), 4.46/4.53/5.54/4.90 (4H,4x s), 4.67 (2H,s), 6.98 (2H,m), 7.21-7.50 (11H,m); MS (APCI+) found (M+1) = 650/652; $C_{35}H_{41}ClFN_5O_2S$ requires 649/651.

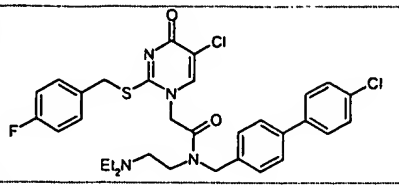
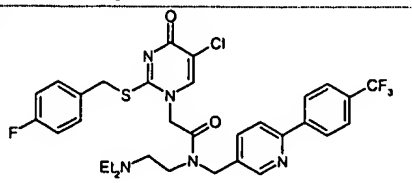
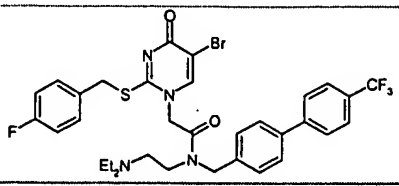
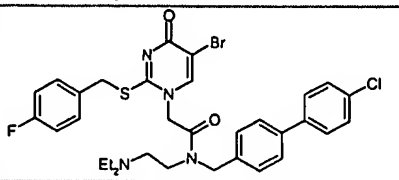
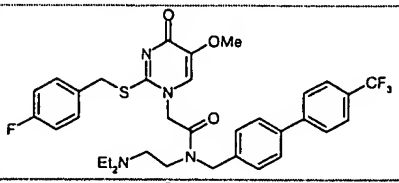
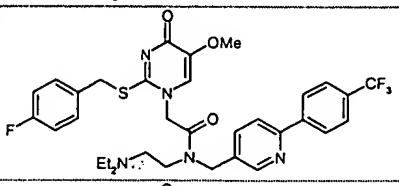
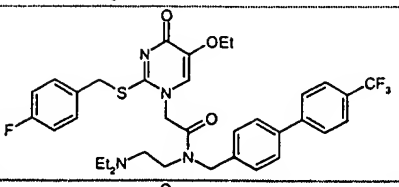
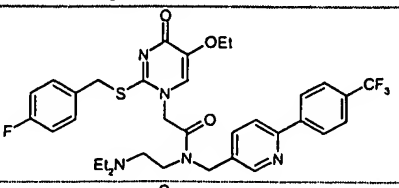
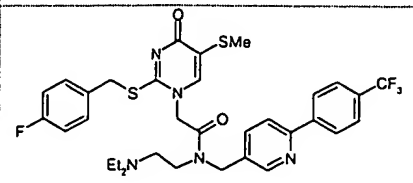
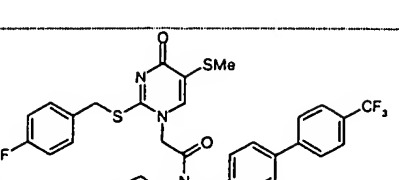
The following Examples were made the method of Example 1 except that in a few cases EDC (2 equiv) and hydroxybenzotriazole (1 equiv) were used in place of HATU and diisopropylamine, in an essentially similar procedure. Where indicated, the salts were subsequently prepared by the methods of Examples 1 or 6 as appropriate:

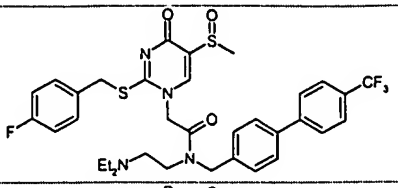
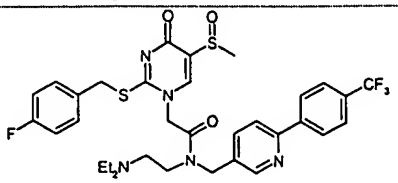
Ex. No.	Precursors	Structure	Name
20	Int. A3 Int. B60		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-methyl-pyrimidin-4-one hydrochloride

21	Int. A26 Int. B60		1-(N-methyl-N-(2-(4-trifluoromethyl-phenyl)pyrid-5-ylmethyl)aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-ethyl-pyrimidin-4-one bitartrate
22	Int. A30 Int. B60		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylpyrimidin-4-one bitartrate
23	Int. A31 Int. B60		1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)-aminocarbonyl-methyl)-2-(4-fluoro-benzyl)thio-5-methylpyrimidin-4-one bitartrate
24	Int. A32 Int. B60		1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-chlorophenyl)pyrimid-5-yl-methyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-methylpyrimidin-4-one bitartrate
25	Int. A33 Int. B60		1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrimid-5-yl-methyl)aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-methylpyrimidin-4-one bitartrate
26	Int. A35 Int. B60		(±)-1-(N-(2-(Diethylamino)ethyl)-N-(1-(4-(4-chlorophenyl)phenyl)ethyl)-amino-carbonyl-methyl)-2-(4-fluorobenzyl)thio-5-methylpyrimidin-4-one bitartrate
27	Int. A34 Int. B60		1-(N-(2-(1-piperidino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-amino-carbonyl-methyl)-2-(4-fluorobenzyl)thio-5-methylpyrimidin-4-one bitartrate
28	Int. A25 Int. B62		1-(N-methyl-N-(4-(4-trifluoromethyl-phenyl)benzyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one
29	Int. A3 Int. B62		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-ethyl-pyrimidin-4-one bitartrate

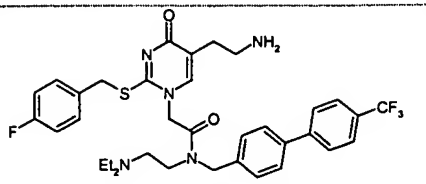
30	Int. A30 Int. B62		1-(N-methyl-N-(2-(4-trifluoromethyl-phenyl)pyrid-5-yl-methyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-ethyl-pyrimidin-4-one
31	Int. A32 Int. B62		1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-chlorophenyl)pyrimid-5-yl-methyl)-amino-carbonyl-methyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one bitartrate
32	Int. A33 Int. B62		1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrimid-5-yl-methyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one bitartrate
33	Int. A3 Int. B63		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-propylpyrimidin-4-one bitartrate
34	Int. A30 Int. B63		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-amino-carbonyl-methyl)-2-(4-fluorobenzyl)thio-5-propylpyrimidin-4-one bitartrate
35	Int. A30 Int. B64		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-ethoxycarbonylmethylpyrimidin-4-one bitartrate
36	Int. A30 Int. B65		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-isopropoxycarbonylmethylpyrimidin-4-one bitartrate
37	Int. A3 Int. B66		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-hydroxy-methylpyrimidin-4-one bitartrate
38	Int. A30 Int. B66		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-amino-carbonyl-methyl)-2-(4-fluorobenzyl)thio-5-hydroxymethylpyrimidin-4-one bitartrate

39	Int. A2 Int. B67		1-(N-methyl-N-(4-(4-chlorophenyl)-benzyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-(2-hydroxyethyl)-pyrimidin-4-one bitartrate
40	Int. A3 Int. B67		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-(2-hydroxyethyl)pyrimidin-4-one bitartrate
41	Int. A31 Int. B67		1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)-aminocarbonyl-methyl)-2-(4-fluoro-benzyl)thio-5-(2-hydroxyethyl)pyrimidin-4-one bitartrate
42	Int. A30 Int. B67		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonyl-methyl)-2-(4-fluorobenzyl)thio-5-(2-hydroxyethyl)pyrimidin-4-one bitartrate
43	Int. A30 Int. B68		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonyl-methyl)-2-(4-fluorobenzyl)thio-5,6-dimethylpyrimidin-4-one bitartrate
44	Int. A3 Int. B69		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one bitartrate
45	Int. A3 Int. B70		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5,6-tetramethylenepyrimidin-4-one bitartrate
46	Int. A30 Int. B70		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-tetramethylenepyrimidin-4-one bitartrate
47	Int. A31 Int. B70		1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)-thio-5,6-tetramethylenepyrimidin-4-one bitartrate
49	Int. A30 Int. B71		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonyl-methyl)-2-(4-fluorobenzyl)thio-5-chloropyrimidin-4-one bitartrate

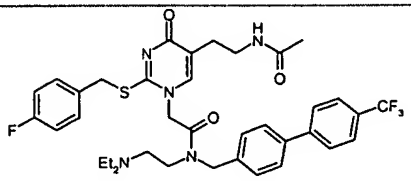
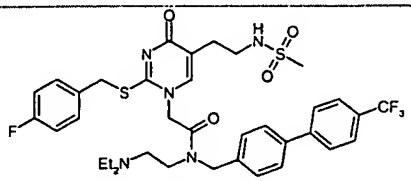
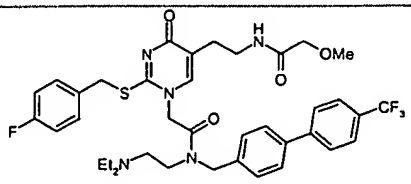
50	Int. A3 Int. B71		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-chloro-pyrimidin-4-one bitartrate
51	Int. A31 Int. B71		1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)-aminocarbonyl-methyl)-2-(4-fluoro-benzyl)thio-5-chloropyrimidin-4-one bitartrate
52	Int. A30 Int. B72		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonyl-methyl)-2-(4-fluorobenzyl)thio-5-bromopyrimidin-4-one bitartrate
53	Int. A3 Int. B72		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)-aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-bromo-pyrimidin-4-one bitartrate
54	Int. A30 Int. B73		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-methoxypyrimidin-4-one bitartrate
55	Int. A31 Int. B73		1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)-thio-5-methoxypyrimidin-4-one bitartrate
56	Int. A30 Int. B74		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethoxypyrimidin-4-one bitartrate
57	Int. A31 Int. B74		1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)-thio-5-ethoxypyrimidin-4-one bitartrate
58	Int. A31 Int. B75		1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)-aminocarbonylmethyl)-2-(4-fluoro-benzyl)thio-5-methylthiopyrimidin-4-one bitartrate
59	Int. A30 Int. B75		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylthiopyrimidin-4-one bitartrate

60	Int. A30 Int. B76		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylsulfinylpyrimidin-4-one bitartrate
61	Int. A31 Int. B76		1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)-thio-5-methylsulfinylpyrimidin-4-one bitartrate

The following compounds were prepared by the method of Example 6:

No.	Precursor	Structure	Name
70	Int. B81		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-aminoethyl)pyrimidin-4-one bitartrate

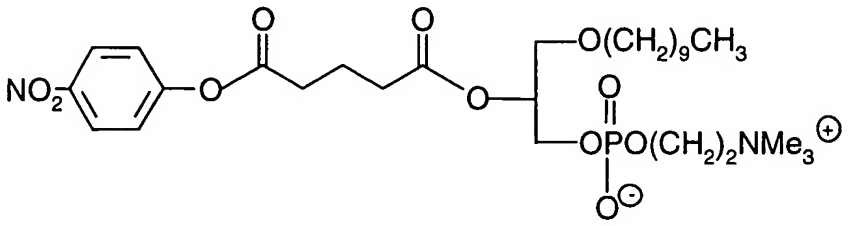
The following compounds were prepared by the method of Example 7:

No.	Precursors	Structure	Name
75	Example 70, acetic anhydride		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-acetamidoethyl)pyrimidin-4-one bitartrate
76	Example 70, methane-sulfonic anhydride		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methanesulfonamidoethyl)pyrimidin-4-one bitartrate
77	Example 70, methoxy-acetyl chloride		1-(N-(2-(Diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-(methoxyacetamido)ethyl)pyrimidin-4-one bitartrate

Biological Data

1. Screen for Lp-PLA$_2$ inhibition.

Enzyme activity was determined by measuring the rate of turnover of the artificial substrate (A) at 37 C in 50mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid) buffer containing 150mM NaCl, pH 7.4.



(A)

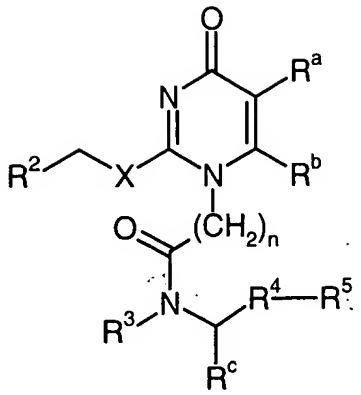
Assays were performed in 96 well titre plates.
Recombinant LpPLA2 was purified to homogeneity from baculovirus infected Sf9 cells, using a zinc chelating column, blue sepharose affinity chromatography and an anion exchange column. Following purification and ultrafiltration, the enzyme was stored at 6mg/ml at 4°C. Assay plates of compound or vehicle plus buffer were set up using automated robotics to a volume of 170µl. The reaction was initiated by the addition of 20µl of 10x substrate (A) to give a final substrate concentration of 20µM and 10 µl of diluted enzyme to a final 0.2nM LpPLA2.
The reaction was followed at 405 nm and 37 °C for 20 minutes using a plate reader with automatic mixing. The rate of reaction was measured as the rate of change of absorbance.

Results

The compounds described in the Examples were tested as described above and had IC_{50} values in the range <0.1nM to 10 µM.

Claims

1. A compound of formula (I):



(I)

in which:

R^a is hydrogen, halogen, $C_{(1-3)}$alkyl, $C_{(1-3)}$alkoxy, hydroxy$C_{(1-3)}$alkyl, $C_{(1-3)}$alkylthio, $C_{(1-3)}$alkylsulphinyl, amino$C_{(1-3)}$alkyl, mono- or di-$C_{(1-3)}$alkylamino$C_{(1-3)}$alkyl, $C_{(1-3)}$alkylcarbonylamino$C_{(1-3)}$alkyl, $C_{(1-3)}$alkoxy$C_{(1-3)}$alkylcarbonylamino$C_{(1-3)}$alkyl, $C_{(1-3)}$alkylsulphonylamino$C_{(1-3)}$alkyl, $C_{(1-3)}$alkylcarboxy, or $C_{(1-3)}$alkylcarboxy$C_{(1-3)}$alkyl;

R^b is hydrogen, halogen, $C_{(1-3)}$alkyl, or hydroxy$C_{(1-3)}$alkyl, with the proviso that R^a and R^b are not simultaneously each hydrogen; or

R^a and R^b together are $(CH_2)_n$ where n is 3 or 4, to form, with the pyrimidine ring carbon atoms to which they are attached a fused 5-or 6-membered carbocyclic ring;

R^c is hydrogen or $C_{(1-3)}$alkyl;

R^2 is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$alkyl, $C_{(1-18)}$alkoxy, $C_{(1-18)}$alkylthio, aryl$C_{(1-18)}$alkoxy, hydroxy, halogen, CN, COR^6, carboxy, $COOR^6$, NR^6COR^7, $CONR^8R^9$, $SO_2NR^8R^9$, $NR^6SO_2R^7$, NR^8R^9, mono to perfluoro-$C_{(1-4)}$alkyl, mono to perfluoro-$C_{(1-4)}$alkoxyaryl, and aryl$C_{(1-4)}$alkyl;

R^3 is hydrogen or $C_{(1-4)}$alkyl which may be unsubstituted or substituted by hydroxy, OR^6, COR^6, carboxy, $COOR^6$, $CONR^8R^9$, NR^8R^9, mono- or di-(hydroxy$C_{(1-6)}$alkyl)amino or N-hydroxy$C_{(1-6)}$alkyl-N-$C_{(1-6)}$alkyl amino;

R^4 is an aryl or a heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$alkyl, $C_{(1-18)}$alkoxy, $C_{(1-18)}$alkylthio, aryl$C_{(1-18)}$alkoxy, hydroxy, halogen, CN, COR^6, carboxy, $COOR^6$, NR^6COR^7, $CONR^8R^9$, $SO_2NR^8R^9$, $NR^6SO_2R^7$, NR^8R^9, mono to perfluoro-$C_{(1-4)}$alkyl and mono to perfluoro-$C_{(1-4)}$alkoxy;

R^5 is an aryl ring which is further optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$alkyl, $C_{(1-18)}$alkoxy, $C_{(1-18)}$alkylthio, aryl$C_{(1-18)}$alkoxy, hydroxy, halogen, CN, COR^6, carboxy, $COOR^6$, $CONR^8R^9$, NR^6COR^7, $SO_2NR^8R^9$, $NR^6SO_2R^7$, NR^8R^9, mono to perfluoro-$C_{(1-4)}$alkyl and mono to perfluoro-$C_{(1-4)}$alkoxy;

R^6 and R^7 are independently hydrogen or $C_{(1-20)}$alkyl, for instance $C_{(1-4)}$alkyl (e.g. methyl or ethyl);

R^8 and R^9 which may be the same or different is each selected from hydrogen, $C_{(1-12)}$alkyl, CH_2R^{10}, $CHR^{11}CO_2H$ or a salt thereof, or R^8 and R^9 together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing one or more further heteroatoms selected from oxygen, nitrogen and sulphur, and optionally substituted by one or two substituents selected from

hydroxy, oxo, $C_{(1-4)}$alkyl, $C_{(1-4)}$alkylCO, aryl, e.g. phenyl, or aralkyl, e.g benzyl, for instance morpholine or piperazine;

R^{10} is COOH or a salt thereof, $COOR^{12}$, $CONR^6R^7$, CN, CH_2OH or CH_2OR^6;

R^{11} is an amino acid side chain such as CH_2OH from serine;

R^{12} is $C_{(1-4)}$alkyl or a pharmaceutically acceptable *in vivo* hydrolysable ester group;

n is an integer from 1 to 4, preferably 1 or 3;

X is O or S.

2. A pharmaceutical composition comprising a compound of formula (I) as claimed in claim 1 and a pharmaceutically acceptable carrier.

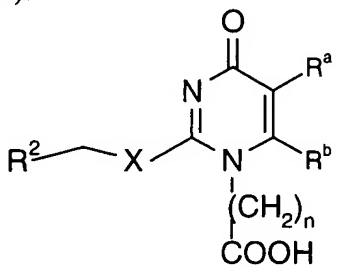
3. A compound of formula (I) as claimed in claim 1 for use in therapy.

4. The use of a compound of formula (I) as claimed in claim 1 for the manufacture of a medicament for treating atherosclerosis.

5. A method of treating a disease state associated with activity of the enzyme Lp-PLA_2 which method involves treating a patient in need thereof with a therapeutically effective amount of a compound of formula (I) as claimed in claim 1.

6. A process for preparing a compound of formula (I) as defined in claim 1 which process comprises:

(a) reacting a compound of formula (II):



(II)

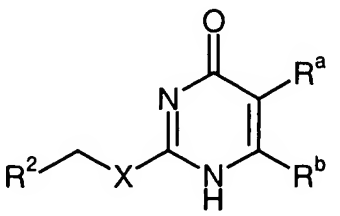
in which X, n, R^a, R^b and R^2 are as hereinbefore defined,
with a compound of formula (III):

$$R^5\text{-}R^4\text{-}CHR^cNHR^3$$

(III)

in which R^c, R^3, R^4 and R^5 are as hereinbefore defined; under amide forming conditions;

(b) reacting a compound of formula (IV):



(IV)

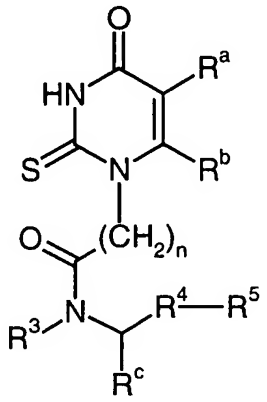
in which X, R^a, R^b and R^2 are as hereinbefore defined,
with a compound of formula (V):

$$R^5\text{-}R^4\text{-}CHR^cNR^3\text{-}CO\text{-}(CH_2)_n\text{-}L^1$$

(V)

in which n, R^3, R^4 and R^5 are as hereinbefore defined, and L^1 is a leaving group such as halogen, for instance bromo or iodo,
in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane;

(c) when X is S, reacting a compound of formula (VI):



(VI)

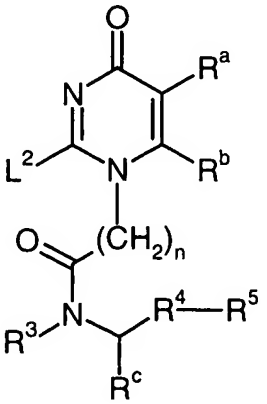
in which n, R^a, R^b, R^c, R^3, R^4 and R^5 are as hereinbefore defined,
with a compound of formula (VII):

$$R^2\text{-}CH_2\text{-}L^1$$

(VII)

in which R^2 and L^1 are as hereinbefore defined,
in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane;

(d) when X is O, reacting a compound of formula (VIII):



(VIII)

in which n, R^a, R^b, R^c, R^3, R^4 and R^5 are as hereinbefore defined, and L^2 is a leaving group such as halogen or alkylthio, for instance methylthio,
with a compound of formula (IX):

$$R^2\text{-}CH_2\text{-}OH \qquad \text{(IX)}$$

in which R^2 is as hereinbefore defined,
in the presence of a base such as 4-dimethylaminopyridine, in an inert solvent such as pyridine; or

(e) converting of compound of formula (I) to another compound of formula (I), by functional group modification, using methods well known to those skilled in the art, for example converting a compound of formula (I) in which R^a is aminoalkyl to a compound of formula (I) in which R^a is alkylcarbonylaminoalkyl, by reaction with an acylating agent, such as, for example, acetic anhydride.